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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08 105,444	08/11/1993	LYNN E. SPITLER	04370003.00	3000

25225 7590 06/11/2003

MORRISON & FOERSTER LLP
3811 VALLEY CENTRE DRIVE
SUITE 500
SAN DIEGO, CA 92130-2332

EXAMINER

GAMBEL, PHILLIP

ART UNIT PAPER NUMBER

1644

DATE MAILED: 06/11/2003

33

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

08/0544

Applicant(s)

SPITLER

Examiner

GAMBEL

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 3/11/03
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) _____ is/are pending in the application. 1-14, 21-40
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) _____ is/are rejected. 1-14, 21-40
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

1. Applicant's amendment, filed 3/11/03 (Paper No. 32), has been entered.
Claims 15-20 have been canceled.
Claims 1, 22 and 23 have been amended.

Claims 1-14 and 21-40 are pending and being acted upon presently.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 3/11/03 (Paper No. 32).
The rejections of record can be found in the previous Office Action (Paper No. 30).

Applicant asserts that the all of the reference filed with the Appeal Brief nor the declaration and references admitted on 5/7/98 have been considered.

In contrast to applicant's assertions and as pointed out in the last Office Action (Paper No. 30), the declarations and Exhibits, filed 5/7/98, have been considered.

In contrast to applicant's reliance on declarations and Exhibits particularly as they read on PSA, applicant is reminded that the rejections under 35 USC 112, first paragraph, do not read on the use of whole PSA, PSMA and PAP but rather read on the scope of antigens encompassed by the claimed invention and the disclosure of the specification as filed.

With respect to applicant's apparent mystification and as pointed out in the last Office Action (Paper No. 30), New Grounds of Rejection were set forth in the last Office Action (Paper No. 30) in order to be consistent with the prosecution in copending USSN 09/300,978.

3. Claims 1-14 and 21-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's arguments, filed 3/11/03 (Paper No. 32), have been fully considered but are not found convincing essentially for the reasons of record and reiterated herein for applicant's convenience.

Applicant asserts that Fiers, Fiddes nor Elil Lilly are applicable to the instant invention. Rather, applicant cites Amgen, Inc. v. Hoeschst Marion Roussel, Inc. 118 (Fed. Cir. 2003). Applicant notes that the court looks to the knowledge in the art and whether the terms are such that an ordinary skilled artisan would comprehend the invention.

Applicant relies upon the disclosure of a genus of antigens useful in the claimed methods, wherein the antigens are defined as over represented (see page 5, lines 15-27) or as immunologically effective portion of antigens (see pages 5-6).

In contrast to applicant's assertions and reliance upon Spittler's Declaration under 37 CFR 1.132 and as pointed out previously, the disclosure of PSA, PSMA and PAP are not sufficient written description of a broad genus of (A) "at least one antigen over represented in the prostate gland or an immunologically effective portion thereof"; (B) "nucleic acid that generate said antigen or antigens in situ", (C) as well as wherein said antigen is a "protein" or a "peptide".

The instant claims are drawn to methods of eliciting antitumor responses to prostate tumors by administering:

A) "at least one antigen over represented in the prostate gland or an immunologically effective portion thereof";

B) "nucleic acid that generate said antigen or antigens in situ",

as well as wherein said antigen is a "protein" or a "peptide".

Such "over represented antigens", "nucleic acid sequences", "proteins" and "peptides" do not meet the written description provision of 35 USC 112, first paragraph. There is insufficient guidance and direction as to the written description of these "over represented antigens", "nucleic acid sequences", "proteins" and "peptides".

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides (proteins) and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus. See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Compliance with the written description requirement is essentially a fact-based inquiry that will "necessarily vary depending on the nature of the invention claimed." Enzo Biochem v. Gen-Probe, Inc. 63 USPQ2d 1609, 1613 (Fed. Cir. 2002) cited in Amgen, Inc. v. Hoeschst Marion Roussel, Inc. Amgen, Inc. v. Hoeschst Marion Roussel, Inc. notes that in Enzo Biochem (63 USPQ2d at 1613), the court clarified that Eli Lilly did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular known structure.

In contrast to relying upon known or minor differences in methodology of producing recombinant proteins as addressed in Amgen, Inc., the instant application does not provide the relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, of "over represented antigens", "immunologically portions thereof", "nucleic acids", "proteins" and "peptides", as they read on prostate antigens other than PSA, PAP or PSMA

Again, it is noted that pages 7-10 of the specification as filed does not provide for over represented prostate antigens other than PSA, PSMA and PAP (see Illustrative Antigens)

Also, it is acknowledged that here the specification discloses certain references for the nucleic acids for PSA, PSMA and PAP; but that such nucleic acid sequences are not disclosed in the specification as file. See Section below

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

In the absence of structural characteristics that are shared by members of the genus of "over represented antigens", "immunologically portions thereof", "nucleic acids", "proteins" and "peptides" as they read on prostate antigens other than PSA, PAP or PSMA encompass by the claimed invention, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Therefore, there is insufficient written description for "at least one antigen over represented in the prostate gland or an immunologically effective portion thereof", "nucleic acid that generate said antigen or antigens in situ", "proteins" or "peptides", other than that disclosed in the specification as filed under the written description provision of 35 USC 112, first paragraph.

Applicant's arguments are not found persuasive.

4. Claims 1-14 and 21-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "full-length PSA, PSMA and PAP"; does not reasonably provide enablement for any "over represented prostate specific antigen", "immunologically effective portion thereof", "protein" or "peptide".

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments, filed 3/11/03 (Paper No. 32), have been fully considered but are not found convincing essentially for the reasons of record and reiterated herein for applicant's convenience.

Again, applicant relies upon the disclosure of a limited number of species (e.g. PSA, PSMA and PAP) and the Spittler declarations under 37 CFR 1.132 and Exhibits to argue that the results of human PSA (Onco Vax P™) to support the in vivo operability and predictability of the claimed invention.

Again and as pointed out above; in contrast to applicant's reliance on declarations and Exhibits particularly as they read on PSA, applicant is reminded that the rejections under 35 USC 112, first paragraph, do not read on the use of whole PSA, PSMA and PAP but rather read on the scope of antigens encompassed by the claimed invention and the disclosure of the specification as filed.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies "over represented prostate antigens", "proteins" or "peptides" other than "PSA, PAP or PSMA". While "over represented prostate antigen" and "immunologically effective portion thereof" may have some notion of the claimed active ingredients; there is insufficient direction and guidance which enables the skilled artisan to make and use "over represented prostate specific antigen" and "immunologically effective portion thereof", commensurate in scope with the claimed invention.

Applicant has not enabled the breadth of the claimed invention in view of the teachings of the specification. Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

Applicant has not disclosed how to use the claimed vaccines and methods to treat prostatic cancer as a therapeutic regimen in humans. There is insufficient evidence of the invention with respect to the in vivo operability of the claimed prostate-specific proteins, peptides or fragments thereof to use appellant's invention.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Concerning vaccines to elicit antitumor responses in general, the antigenic or immunogenic nature of a protein does not necessarily correlate with its ability to confer antitumor responses.

As disclosed on page 2, paragraph 1 of the instant specification; applicant discloses that prostate cancer continues to be refractory to treatment despite many years of efforts to improve therapy. Similarly, appellant discloses that at the time the invention was made; vaccine development has been slow and no vaccine approved by the FDA for marketing currently exists for any form of cancer.

Applicant has not provided sufficient objective evidence that predicts the efficacy of the instant invention drawn to "over represented prostate antigens" or "immunologically active portions of PSA, PSMA or PAP" in the specification as filed or a portion thereof for the treatment or prevention of human prostatic cancer.

While applicant asserts the applicant's cited reference mischaracterizes Spittler's point and that the active components of vaccine are identified and purified are now available for routine vaccine protocols. However, the specification as filed does not appear to identify and purify over represented prostate antigens other than PSA, PSMA and PAP. In addition, applicant argues that Hodge, Ezzel do not support the lack of unpredictability.

As the instant inventor acknowledges (Spittler, Cancer Biotherapy 10:1-3, 1995; page 1, column 1, paragraph 1; 1449); "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company, and you're likely to get the same response". Therefore, applicant has recognized the lack of predictability of the nature of the art and state of the prior art to which the instant invention pertains, as similarly disclosed on page 2 of the specification. Also, such disclosures clearly indicate that the amount of direction or guidance presented in the specification is limited, and would not permit a person skilled in the art to use the invention without undue experimentation at the time the invention was made.

Applicant's application may provide a plan to vaccinate against prostate tumors, there is insufficient guidance and direction as to those over represented antigens, portions, proteins and peptides other than PSA, PSMA and PAP in a clearly unpredictable field of endeavor, namely the tumor vaccination in the absence of identifying the characterizing those critical elements that would lead to the appropriate responses, particularly in the absence of working examples. Applicant's reliance on the certain working examples such as PSA is consistent with the rejection of record and the references of record.

Furthermore, Hodge et al. (Int. J. Cancer 63: 231-237, 1995; 1449) discloses that previous attempts to actively immunize patients with prostate adenocarcinoma cells admixed with adjuvant shown little or no therapeutic benefit (page 231, column 1, first paragraph of Introduction). Here, the reference discloses that these previous attempts to actively immunize were known in 1990, prior to appellant's invention. Such prostate adenocarcinoma cells and normal prostate cells express common antigens. Therefore, targeting prostate-specific antigens that are expressed on both normal and tumor cells in cancer immunotherapy to target tissue-specific antigens was known and practiced at the time the invention was made.

With respect to prostate-specific immunotherapy, Hodge et al. (Int. J. Cancer, 1995; 1449) discloses that previous attempts to actively immunize patients with prostate adenocarcinoma cells admixed with adjuvant shown little or no therapeutic benefit (page 231, column 1, first paragraph of Introduction). Models of evaluation of prostate therapeutics including the canine and the Dunning rat are not practical for PSA-recombinant vaccines due to the very low homology of rat and canine PSA to human PSA (page 231, column 2, paragraph 2). The fact that human PSA is a secreted antigen should be taken into consideration for its potential use as a target for human prostate cancer, as the secreted antigen may also reduce immunoglobulin responses by forming antigen-antibody complexes and/or potentially anergizing specific T cell responses (page 235, column 1, lines 1-6). An immune reaction directed against PSA could lead to side effects resulting from cross-reactivity with other kallikrein family members (page 235, column 2, lines 4-6). Therefore, the use of prostate-specific antigens in vaccines are likely to be limited by either neutralization by secreted prostate antigen or by inducing autoimmunity. Although the recombinant human PSA construct was unable to elicit an anti-PSA IgG response, PSA-specific IgM response were noted in all immunized monkeys (page 236, column 1, paragraph 1). However, these antibody responses were of low titer, were short-lived and could not be boosted. It is noted that the monkeys developed in vitro lymphoproliferative responses to PSA (page 236, column 1, paragraph 2). However, it is not clear that such studies can be extrapolated to humans because in the difference in MHC motifs between rhesus and humans and the levels of expression of class I and II MHC on rhesus vs. human prostate and human normal prostate vs. prostate carcinoma (page 236, column 2, last paragraph). In addition to these cautions with respect to appropriate antigen presentation and subsequent immune responses (issue of MHC), this reference clearly indicates limited antibody responses and only some level in vitro cellular immunity with prostate specific antigen immunization. Also, this reference clearly indicates the limitations of animal models in prostate cancer modalities and that previous attempts at human prostate cancer vaccination with whole cells.

Full enablement of claims on vaccines should include teachings on the relevant immunogenic proteins and portions thereof, the level of neutralizing antibody or cellular immunity produced and the efficacy of the vaccine against subsequent inoculations of the intended pathogen, in this case a prostate tumor. Since the immune response is considered to be one of the most complex and unpredictable biological processes, without any guidance or teachings of any of the above, it is considered that it would require undue experimentation for the ordinary skilled artisan to make or to use the invention as claimed.

With respect to "immunologically effective portion thereof", the instant claims are not enabled for the breadth of "immunologically effective portion thereof". The characteristics of these antigens or portions are not clearly defined and encompasses potentially thousands of different polypeptides and peptides. The specification fails to provide sufficient guidance as to how to determine all such polypeptides and peptides. It would require undue experimentation to produce all such possible polypeptides and peptides without more explicit guidance from the disclosure.

The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. Ezzell reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (J. NIH Research 7: 46-49, 1995; see entire document, particularly the last paragraph; 1449). It has been well known in the art that tumor cells in vivo simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes (Ezzell; page 48, column 2, paragraph 2). Furthermore, no one is very optimistic that a single peptide or a virus carrying the gene encoding that peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (Ezzell; page 48, paragraph 6).

With respect to inducing prostate tumor-specific cytotoxic T lymphocytes; Peshwa et al. (The Prostate 36: 129-138, 1998) discloses that the protein sequence of PAP was evaluated using an algorithm to detect contiguous 9-amino acid peptide stretches which could potentially bind the HLA-A2 molecule; that various binding affinities were noted among the tested peptides, resulting in PAP-5 epitope as the most relevant for PAP-based therapeutic vaccines for prostate cancer (see Results); and that of the five nonapeptides shown to exhibit strong binding affinity for the HLA-A2 molecules, only PAP-5 is contained with the mature secreted PAP protein (page 136, column 1, paragraph 1).

While page 12 of the specification discloses screening for identifying peptides which may be important epitopes; applicant has not provided sufficient direction and guidance nor objective evidence in identifying or identification with "immunologically effective portions" of "over represented prostate antigens, including PSA, PSMA, PAP".

While Peshwa et al. (The Prostate, 1998) discloses that similar approaches employing dendritic cells loaded with HLA-A2 binding peptides of PSMA have been reported to have a clinical benefit (see Discussion); it appears that undue experimentation would be required of one skilled in the art to practice the claimed methods and compositions in providing effective vaccines for prostatic cancer using the teaching of the specification alone.

Insufficient direction or guidance is provided to assist one skilled in the art in the selection of all such possible "over represented antigens" and/or "immunologically active portions thereof, including PSA, PSMA and PAP" nor is there sufficient objective evidence provided that all such "antigens" and "immunologically active portions thereof" would be effective to stimulate antitumor responses .

The specification does not provide a sufficient enabling description of the claimed invention. There is insufficient direction and guidance to enable a skilled artisan to make and use "over represented antigens", "immunologically active portions thereof", "proteins" and "peptides", as recited in the claims. A person of skill in the art would not know which "over represented antigens", "immunologically active portions of said over represented antigens, including PSA, PAP, and PSMA", "proteins" and "peptides" are essential or effective to stimulate antitumor responses, which "antigens"/"portions thereof" are non-essential or noneffective, and what particular lengths identify essential or effective portions. The problem of predicting polypeptide structure from mere sequence data of limited full length prostate antigens sequences and, in turn, utilizing predicted structural determinations to ascertain immunologically active portions of over represented prostate antigens and finally what changes can be tolerated with respect thereto and, in turn, which stimulate antitumor responses is complex and well outside the realm of routine experimentation.

In view of the lack of predictability of the art to which the invention pertains and the lack of established clinical protocols for effective cancer vaccines and prostate cancer therapies; undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for establishing protective antitumor responses.

Applicant's arguments are not found persuasive.

5. Claims 1, 2, 4-8, 10-14, 20-22, 24-28, 30-34, and 37-40 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's arguments, filed 3/11/03 (Paper No. 32), have been fully considered but are not found convincing essentially for the reasons of record and reiterated herein for applicant's convenience.

Applicant argues that the instant specification provides an expressed teaching of what constitutes an over represented antigen on page 5, lines 15-27, using well known and convention assessments of therapeutic toxicity.

However, it is noted that the specification here also defines the term "over represented in relative terms by disclosing:

"By "over represented" is meant that the concentration of this antigen in prostate is sufficiently higher than its concentration in any other tissue such that the prostate can effectively be targeted by the immune response raised against this antigen with relative sparing of other organs or tissues."

Claims , 2, 4-8, 10-14, 20-22, 24-28, 30-34, and 37-40 are indefinite in the recitation of "over represented antigens" because the term "over represented" is a relative term which renders the claims indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

6. Claims 1-14 and 21-40 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Spitler (U.S. Patent No. 5,738,867 in view of Israeli et al. (U.S. Patent No. 5,538,866), Horoszewicz (U.S. Patent No. 5,162,504), Andriole et al. (Ann. Rev. Med. 42: 9-15, 1991) and in view of art acknowledged methods of delivering antigens of interest to stimulate antitumor responses, as disclosed on pages 10-19 of the instant specification and in further evidence of McCarley et al. (Seminars in Surgical Oncology 5:293-301, 1989).

Applicant's arguments, filed 3/11/03 (Paper No. 32), have been fully considered but are not found convincing essentially for the reasons of record and reiterated herein for applicant's convenience.

Applicant argues that the combination of references must provide motivation to combine the teachings of these references to result in claimed methods by providing a reasonable expectation of success.

Curiously, applicant asserts that the Office seems to rely on the assumption that a demonstration that any one tumor antigen can elicit an immune response of any kind results in the claimed methods using over represented prostate antigens to elicit an anti-prostate tumor response. In contrast, it appears that applicant relies upon this assertion to counter the rejections under 35 USC 112, first paragraph. It is noted that such 112, first paragraph, rejections address the scope of "over represented prostate antigens" and "fragments thereof" which are not identified and characterized in the application as filed.

In contrast to applicant's assertions, the art rejection of record does provided sufficient motivation and expectation of success vaccinating with prostate antigens, including applicant's own prior art.

Applicant argues that Spitler teaches the use of antigens that are uniquely associated with the malignant or metastatic nature of the cells and disclose only two antigens. Applicant argues that Spitler teaches the use of a pan-epitope to stimulate a general antitumor immune response against any malignant cells, however applicant has not pointed out where Spitler provides such a teaching or such a limited teaching.

In contrast to applicant's assertions, Spitler teaches methods of delivering antitumor vaccines with tumor associated antigens, including prostate antigens (see Summary of the Invention), as well as known methods of delivering said tumor associated antigens to stimulate antitumor responses, encompassed by the claimed invention (see entire document). Spitler teaches that patients with cancer may have the cancer surgically excised and then be given the subject tumor vaccines (see column 10, lines 39-47).

Applicant's distinction between active and passive immunotherapy is acknowledged.

The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and not is it that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). See MPEP 2145.

In response to applicant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, Spitler teaches methods of delivering antitumor vaccines with tumor associated antigens, including prostate antigens (see Summary of the Invention) and the teachings of secondary references that PSMA was associated with prostate tumors and, in turn, was a targeted prostate tumor antigen would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art, namely immunizing individuals with PSMA as a prostate tumor associated antigen. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144

A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." See In re Gurley, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994).

Here in contrast to applicant's assertions of teaching away by the prior art because the references indicate a successful method of active immunization with prostate tumor associated antigens and that PSMA was a prostate tumor associated antigen at the time the invention was made; there was no discouragement nor skepticism in the prior art for active immunization with prostate tumor associated antigens, nor that PSMA was a prostate tumor associate antigen at the time the invention was made.

Spitler differs from the instant claimed methods by not disclosing a particular prostate antigen, nor the species PSMA per se.

Israeli et al. teach PSMA , including nucleic acids and methods of expressing said PSMA, as well as its expression on prostate tumors (see entire document, including Background of the Invention and Detailed Description of the Invention). Israeli et al. teach that the main metastatic site for prostatic tumor is the bone (column 23, paragraph 2).

Horszewicz (U.S. Patent No. 5,162,504) teaches that there is a need for monoclonal antibodies which are prostate specific and which do not cross react with other tissue types (see column 6, paragraph 2 and provides for the monoclonal antibodies specific for prostatic tumor antigens and distinguishable from prior prostate antigens (see entire document, including Summary of the Invention and Claims). Horszewicz further discloses that prostatic epithelium has limited distribution, does not carry out functions vital for the survival of a patient and has been shown to produce organ specific molecules (see column 3, paragraph 3). In addition, the evidence for the selective specificity for the 7E11-C5 for human prostatic epithelium was reinforced by consistently negative results of immunospecific staining of numerous fresh frozen sections from a wide range of human non-prostatic normal or malignant tissues (see column 24, paragraph 3 and Results).

Andriole et al. review the diagnosis and treatment of prostate cancer and teach that surgical excision of the prostate is unsurpassed as a means of controlling organ-confined prostate cancer (see page 13, paragraph 2).

McCarley et al. teach that in prostate cancer, monoclonal antibodies prostate antigens are not usually tumor specific (See Abstract and page 298, column 2, paragraph 3 - page 299).

Pages 10-19 of the specification discloses the art known methods of delivering antigens, including tumor associated antigens, such as expression systems, anti-idiotypic antibodies, vaccines formulations of interest to stimulate anti-tumor responses encompassed by the claimed methods and vaccines.

Given the teachings of Israeli et al. and Horszewicz that the PSMA / 7E11 specificity is a marker or antigen for prostate cancer; one of ordinary skill in the art at the time the invention was made would have been motivated to substitute the prostate tumor associated antigen PSMA into the methods of stimulating antitumor responses, as known and practiced in the prior art, as taught by Spitler and acknowledged by the specification as to treat prostate cancer.

Given the tissue and tumor specificity of the PSMA / 7E11 specificity as well as immunogenicity as well as its advantages over previous prostate antigens taught by Israeli and Horoszewicz coupled with McCarley et al. teaching that in prostate cancer, monoclonal antibodies prostate antigens are not usually tumor specific (See Abstract and page 298, column 2, paragraph 3 - page 299); one of ordinary skill in the art at the time the invention was made would have been motivated to apply the PSMA prostate antigen in the methods of Spitler to elicit antitumor responses to prostate antigens. It would have been obvious to the ordinary artisan to use PSMA in patients with metastatic prostate tumors and/or patients who have had the prostate tumor removed surgically to elicit antitumor responses in order to treat said cancer patients.

Again, Spitler teaches that patients with cancer may have the cancer surgically excised and the be given the subject tumor vaccines (see column 10, lines 39-47) and Andriole et al. teach that surgical excision of the prostate is unsurpassed as a means of controlling organ-confined prostate cancer (see page 13, paragraph 2).

Also, it would have been obvious to the ordinary artisan to select portions, particularly extracellular portions of PSMA to stimulate antitumor responses. From the teachings of the references and known in the prior art; it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments are not found persuasive.

7. Claims 1-14 and 21-40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 5,925,362. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the patented claims, drawn to PSA read as a species on the instant methods and vaccines to treat prostate tumors.

Applicant's amendment, filed 3/11/03 (Paper No. 32), request that this rejection be held in abeyance until the above-identified issues have been resolved.

This rejection is maintained.

8. Claims 1-14 and 21-40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13, 15, 16, 18-24 (or appropriate pending claims) copending application Serial No. 09/300,978. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending claims drawn to PSMA read on a species of the instant methods and vaccines to treat prostate tumors.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's amendment, filed 3/11/03 (Paper No. 32), does not comment on this rejection.

This rejection is maintained.

9. No claim is allowed.

10. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.



Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
June 6, 2003